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Losartan Improves Exercise Tolerance in Patients With Diastolic Dysfunction and a Hypertensive Response to Exercise

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OBJECTIVES The aim of the study was to test the hypothesis that angiotensin II (Ang II) blockade would improve exercise tolerance in patients with diastolic dysfunction and a marked increase in systolic blood pressure (SBP) during exercise.

BACKGROUND Diastolic dysfunction may be exacerbated during exercise, especially if there is a marked increase in SBP. Angiotensin II may contribute to the hypertensive response to exercise and impair diastolic performance.

METHODS We performed a randomized, double-blind, placebo-controlled, crossover study of two weeks of losartan (50 mg q.d.) on exercise tolerance and quality of life. The subjects were 20 patients, mean age 64 ± 10 years with normal left ventricular systolic function (EF >50%), no ischemia on stress echocardiogram, mitral flow velocity E/A <1, normal resting SBP (<150 mm Hg), and a hypertensive response to exercise (SBP >200 mm Hg). Exercise echocardiograms (Modified Bruce Protocol) and the Minnesota Living With Heart Failure questionnaire were administered at baseline, and after each two-week treatment period, separated by a two-week washout period.

RESULTS Resting blood pressure (BP) was unaltered by placebo or losartan. During control, patients were able to exercise for 11.3 ± 2.5 (mean ± SD) min, with a peak exercise SBP of 226 ± 24 mm Hg. After two weeks of losartan, baseline BP was unaltered, but peak SBP during exercise decreased to 193 ± 27 mm Hg ($p < 0.05$ vs. baseline and placebo), and exercise time increased to 12.3 ± 2.6 min ($p < 0.05$ vs. baseline and placebo). With placebo, there was no improvement in exercise duration (11.0 ± 2.0 min) or peak exercise SBP (217 ± 26 mm Hg). Quality of life improved with losartan (18 ± 22, $p < 0.05$) compared to placebo (22 ± 26).

CONCLUSIONS In patients with Doppler evidence of diastolic dysfunction at rest and a hypertensive response to exercise, Ang II receptor blockade blunts the hypertensive response to exercise, increases exercise tolerance and improves quality of life. (J Am Coll Cardiol 1999;33:1567–72) © 1999 by the American College of Cardiology

Many elderly subjects and patients with hypertension or left ventricular (LV) hypertrophy have Doppler echocardiographic evidence of impaired diastolic function, but do not have any symptoms of heart failure at rest (1–3). The ability to increase the cardiac output during exercise without an abnormal elevation in left atrial pressure depends on the capacity of the left ventricle to enhance its diastolic filling (4). Thus, it is likely that diastolic dysfunction may limit exercise tolerance before resulting in symptoms at rest.

Elevated systolic arterial blood pressure (BP) impairs diastolic performance. This is dramatically apparent in patients who develop flash pulmonary edema in association with a marked increase in systolic BP (SBP) (>200 mm Hg) (5). Lowering the arterial pressure produces a rapid resolution of the pulmonary edema. Systolic arterial pressure normally increases during exercise. In elderly and hypertensive subjects the increase in systolic arterial pressure during exercise is frequently exaggerated (6–8). The exercise-induced increase in systolic arterial pressure may be partially mediated by angiotensin II (Ang II), whose circulating levels increase during exercise (9). Furthermore, Ang II impairs LV relaxation (10). This effect may be accentuated in the failing heart and also in hypertrophied myocardium (10–12). These observations suggest that blocking the generation or action of Ang II could improve diastolic function during exertion, thus enhancing exercise tolerance.

Accordingly, we performed a randomized, double-blind, placebo-controlled, crossover study of the Ang II receptor

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
Ang II = angiotensin II
BP = blood pressure
IVRT = isovolumetric relaxation time
LV = left ventricular
SBP = systolic blood pressure

blocker, losartan, on exercise tolerance and quality of life in patients with Doppler-echocardiographic evidence of mildly impaired diastolic performance and a marked hypertensive response to exercise.

METHODS

Patient population. Twenty-one subjects were recruited from patients undergoing exercise testing for the evaluation of coronary artery disease as the cause of exertional dyspnea. Entry criteria included left ventricular ejection fraction >50% by 2-D echocardiography, no evidence of myocardial ischemia on stress echocardiogram, no valvular heart disease, resting SBP ≤150 mm Hg, mitral valve Doppler flow pattern with peak E wave less than peak A wave velocity (E/A <1.0), and peak SBP >200 mm Hg during exercise. Patients taking an Ang II receptor blocker were excluded, whereas patients taking other medications were not excluded. Patients with other diseases that could limit exercise tolerance were excluded.

Protocol. Each subject provided informed, written consent to the protocol that had been approved by our institutional review board. All baseline medications were continued during the study. Baseline serum electrolytes, resting 2-D echocardiogram, and Doppler measurements of mitral valve flow velocities were obtained. The subjects completed the Minnesota Living With Heart Failure questionnaire (13), modified to assess symptoms over the preceding two weeks. The subjects then underwent a baseline treadmill exercise test using the modified Bruce Protocol (14). Blood pressure was obtained using a sphygomanometer at the end of each 3-min stage. Immediately after exercise the Doppler-echocardiogram was repeated. The patients were randomly assigned to receive placebo or 50 mg of losartan in identical gelatin capsules each morning upon awakening. Both investigators and the subjects were unaware of the assignment. After two weeks, the treadmill exercise test and baseline studies were repeated 2 to 4 h after taking the study medication. Then the study medication was discontinued for two weeks, and the patients then crossed over to placebo or losartan. After two weeks of therapy, the studies were repeated.

Echocardiogram. Resting LV volumes and ejection fraction were measured from the apical four-chamber view using the modified Simpson's rule method (15). Left ventricular mass was calculated using the area length method (15). The transmitral flow velocity was measured using pulsed-wave Doppler with the sample volume positioned between the mitral leaflet tips during diastole (16). The E wave and A wave peak velocities, the ratio of the E wave to A wave peak velocities (E/A ratio), E wave deceleration time, and the isovolumetric relaxation time (IVRT) were measured on three separate beats and then averaged. The transmitral Doppler measurements were measured at rest and immediately postexercise.

Statistical analysis. Data are expressed as mean ± SD. Analysis of variance of repeated measures was used to compare the initial control, placebo and losartan values. Between-group comparisons were performed using the Tukey test. The level of significance was taken as $p < 0.05$. Because the Minnesota Living With Heart Failure score is not normally distributed, the placebo and losartan scores were compared using the Wilcoxin signed rank-sum test (17).

RESULTS

Patient characteristics. Twenty-one patients entered the study. One patient experienced an increase in serum creatinine from 1.5 to 2.0 mg/dl while receiving the initial study medication (losartan). The patient was withdrawn from the study. No other subject developed any abnormality of serum electrolytes or creatinine. Twenty patients completed the study: 4 men and 16 women. The mean age was 64 ± 10 years (range 53 to 79 years). Sixteen patients had a past history of hypertension but had resting SBP ≤150 mm Hg on medications at the time of entry into the study (Table 1). Seven patients were taking beta-blockers, six were taking diuretics, five were taking calcium blockers, and six were taking angiotensin-converting enzyme (ACE) inhibitors. Resting BP was well controlled (143/79 ± 8/8 mm Hg) at baseline. The patients exercised for 11 ± 2.5 min on the initial exercise test, stopping because of dyspnea or fatigue. No patient experienced angina. The peak SBP during exercise was 226 ± 24 mm Hg and was greater than 200 mm Hg in all patients (an entry criteria).

Baseline Doppler echocardiographic results. The resting LV end-diastolic volume was 87 ± 26 ml, the LV end-systolic volume was 36 ± 16 ml, the ejection fraction was 0.60 ± 0.10, and the LV mass was 90 ± 26 gm/m^2. Five patients had LV hypertrophy (LV mass >110 gm/m^2). The resting mitral valve E/A ratio was 0.75 ± 0.13 and less than 1.0 in all subjects (an entry criteria). The E/A ratio increased after exercise to 0.91 ± 0.19 ms ($p < 0.05$) and the E deceleration time decreased from 197 ± 31 ms to 172 ± 30 ms ($p < 0.05$) (Table 2).

Table 1. Patient Characteristics

Patient	Gender/Age (yrs)	Systolic BP		Exercise Time (min)	Medications			
		Rest (mm Hg)	Exercise (mm Hg)		Beta-Blocker	Diuretic	Calcium-Blocker	ACE-I
1	F/69	142	264	9				
2	F/62	148	224	12				x
3	F/75	148	226	9.5	x	x		
4	F/42	130	224	12			x	
5	M/70	150	212	14	x			
6	F/70	142	264	13			x	
7	F/79	150	206	14	x	x		
8	F/47	150	208	11		x		
9	F/60	140	286	10		x		x
10	F/72	140	244	8	x	x		
11	F/71	148	236	11				
12	F/62	150	210	13	x			
13	F/51	140	202	14			x	x
14	M/58	128	208	13			x	
15	F/69	146	206	12				x
16	M/70	150	222	7	x			x
17	F/75	142	210	8	x			x
18	M/53	140	218	14			x	
19	F/57	120	244	15				
20	F/70	150	204	7		x		
Mean	64	143	226	11				
SD	10.1	8.4	24	2.5				

Effect of placebo and losartan in exercise parameters. The resting systolic and diastolic pressures were unaltered by placebo or losartan compared with control (Table 3; Fig. 1). The exercise time was similar during baseline (11.3 ± 2.5 min) and placebo (11.0 ± 2.0) but significantly ($p < 0.05$) increased during losartan (12.3 ± 2.6 min). In 16 of the 20 patients, exercise time was longer on losartan than placebo, in two patients it was identical, and in two others exercise time was longer on placebo by one min. Both systolic and diastolic BP readings at rest were not altered by losartan or placebo. However, peak SBP during exercise was reduced on losartan to 193 ± 27 mm Hg compared to placebo (217 ± 26, $p < 0.05$) and baseline (226 ± 24 mm Hg, p = NS). Similarly, the exercise time required to achieve a SBP >190 mm Hg was delayed on losartan to 10.6 ± 3.3 min compared to placebo (8.7 ± 3.5 min, $p < 0.05$), which was similar to baseline (7.5 ± 3.3). Peak heart rate was unaffected by losartan. Quality of life assessed by the modified Minnesota Living With Heart Failure score improved to 18 ± 22 on losartan compared with placebo (22 ± 26, $p < 0.05$), which was similar to baseline (25 ± 22). Similarly, using only the questions directly assessing exercise tolerance, the score improved on losartan (5.2 ± 7.3) compared to placebo (9.9 ± 7.7, $p < 0.05$), which was similar to control (9.9 ± 7.9).

Neither losartan nor placebo had any significant effect on LV end-diastolic volume, IVRT, mitral E/A ratio, or E-wave deceleration (Table 4). They also had no effect on resting SBP or heart rate.

DISCUSSION

We studied patients with diastolic dysfunction manifested by an altered Doppler-echocardiographic pattern of LV filling with a reduced mitral valve E wave and enhanced A wave. This "impaired relaxation pattern" of LV filling is an early manifestation of abnormal LV diastolic performance (2,3). In our subjects, the abnormal LV filling pattern resulted from hypertension, LV hypertrophy, or the normal aging process (18). The patients had normal LV ejection fractions, and none of the patients had evidence of exercise-induced myocardial ischemia. All of our patients were asymptomatic at rest but had dyspnea with exertion. After exercise the mitral valve E/A ratio increased, and the E wave deceleration time shortened. These changes are consistent with an increase in left atrial pressure (19). Such an increase in left atrial pressure with exercise may have contributed to the patients' exertional dyspnea. The addition of an angiotensin AT_1-receptor blocker, losartan, to the patients' medications improved our subjects' ability to walk on a treadmill by approximately 1 min using the Modified Bruce Protocol. The improvement in treadmill exercise time was also manifest as an increase in quality of life and exercise tolerance as measured by the Minnesota Living With Heart Failure questionnaire (13). These improvements occurred despite

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Table 2. Baseline Doppler Echocardiographic Characteristics

Patient	Mitral Valve E/A		E Deceleration Time		LV Volumes			
	Rest	Exercise	Rest (ms)	Exercise (ms)	End-Diastolic (ml)	End-Systolic (ml)	Ejection Fraction	LV Mass (g/m^2)
1	0.51	—	255	—	88	43	0.51	73
2	0.98	0.98	175	205	111	44	0.60	61
3	0.74	1.23	220	115	50	15	0.70	135
4	0.75	0.90	200	170	129	54	0.58	58
5	0.67	1.05	195	185	105	30	0.71	85
6	0.79	0.73	210	172	85	40	0.53	58
7	0.83	0.92	186	225	37	5	0.86	75
8	0.81	0.83	165	213	97	42	0.57	69
9	0.85	0.94	205	215	94	44	0.53	90
10	0.88	0.88	170	144	55	13	0.76	73
11	0.77	0.91	155	165	52	17	0.67	97
12	0.92	1.04	170	145	68	34	0.50	69
13	0.54	0.60	160	—	125	61	0.51	127
14	0.68	0.78	175	165	114	56	0.51	86
15	0.65	0.85	168	140	70	31	0.56	133
16	0.52	1.48	205	135	101	46	0.54	117
17	0.63	0.75	260	150	100	44	0.56	132
18	0.73	0.78	200	185	103	48	0.53	97
19	0.86	0.87	230	190	81	30	0.63	68
20	0.81	0.83	240	184	83	32	0.61	92
Mean	0.75	0.91*	197	172*	87	36	0.60	90
SD	0.13	0.19	31	30	26	16	0.10	26

*$p < 0.05$ vs. rest.

relatively good exercise tolerance (11.3 ± 2.5 min), mild symptoms and normal SBP at baseline.

Mechanism. What is the mechanism of the losartan-induced improvement of exercise tolerance in our study? Two weeks of losartan therapy did not alter any Doppler-echocardiographic measure of LV diastolic performance (mitral E/A, IVRT or deceleration time) at rest. Thus, a change in the baseline diastolic function is not the mechanism of losartan's action. However, a longer course of therapy might have produced improvement in diastolic function by inducing regression in patients with LV hypertrophy.

Despite well-controlled BP at rest, our patients had an increase in SBP to >200 mm Hg during exercise prior to treatment with losartan. Such systolic hypertension during exercise is common (perhaps typical) in subjects over 60 and occurs in many patients with hypertension even when BP is well controlled at rest (6,8). An increase in arterial systolic pressure increases LV afterload, thus slowing LV relaxation and reducing the extent of ejection. The ventricle operates at higher volumes (utilization of preload) and there is an increase in left atrial pressure in response to increased systolic load (20). Although losartan did not reduce resting BP, it slowed the increase in SBP during exercise and decreased the peak SBP by a mean of 33 mm Hg. It is likely that the decrease of SBP during exercise contributed to the improvement in exercise tolerance with losartan. Our findings also demonstrate the role of Ang II acting through AT_1 receptors, in contributing to the increase in SBP during exercise. Although our patients did not have clinical evidence of exercise-induced myocardial ischemia, it is possible that losartan improved endothelial function, allowing for improved coronary perfusion.

Table 3. Effect of Placebo and Losartan on Exercise Parameters

	Baseline	Placebo	Losartan
Exercise time (min)	11.3 ± 2.5	11.0 ± 2.0	12.3 ± 2.6*†
Resting systolic BP	143 ± 8	140 ± 21	138 ± 14
Resting diastolic BP	79 ± 8	77 ± 7	76 ± 7
Peak systolic BP (mm Hg)	226 ± 24	217 ± 26	193 ± 27*†
Time to BP >190 (min)	7.5 ± 3.3	8.7 ± 3.5	10.6 ± 3.3*†
Heart rate (BPM)	141 ± 15	139 ± 20	135 ± 20
Minnesota Living With Heart Failure Score	25 ± 22	22 ± 26	18 ± 22*

*$p < 0.05$ (Placebo vs. Losartan). †$p < 0.05$ (Losartan vs. Baseline). Values are mean ± SD.

Angiotensin II slows the rate of LV relaxation and increases LV diastolic pressures (10). Thus, some of the beneficial effect of losartan in our study may have been due to blocking the effect of Ang II on LV relaxation during exercise. Because ACE inhibitors do not prevent the increase in circulating Ang II that occurs during exercise (9), it is possible that ACE inhibition may not produce the same

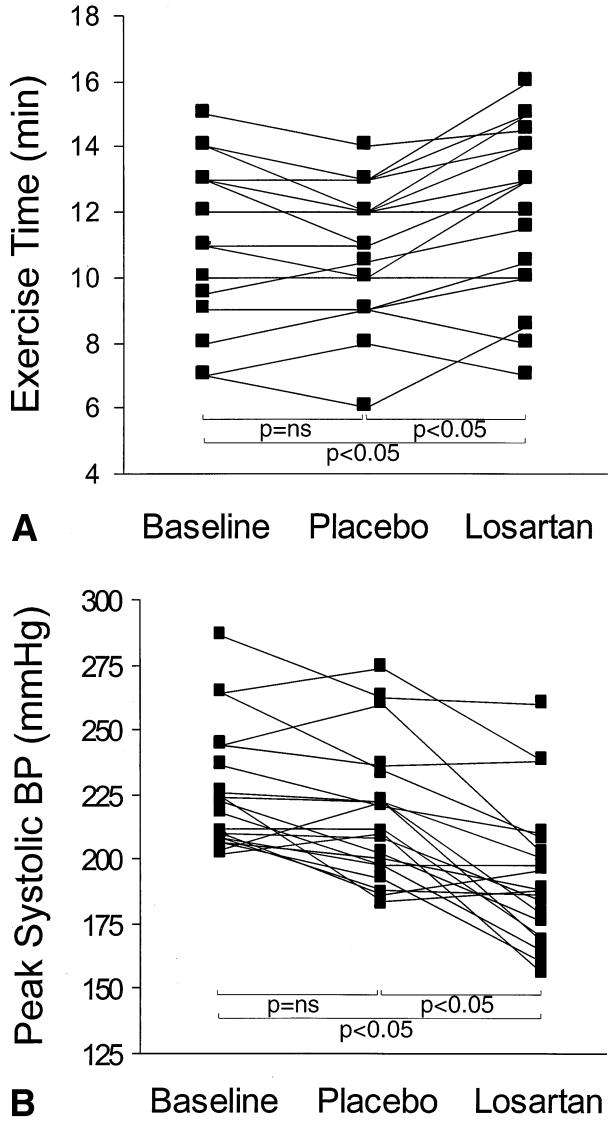

Figure 1. Plot of exercise duration **(A)** and peak systolic blood pressure (BP) **(B)** during baseline and during treatment with placebo and losartan. Treatment with losartan increased exercise time and reduced peak systolic BP during exercise compared to baseline and placebo.

beneficial effects seen with an Ang II receptor blocker in our study.

Comparison to previous studies. There are few studies of therapy of diastolic dysfunction to compare to our results. Similar to our observations with two weeks of losartan therapy, Setaro et al. (21) found that five weeks of therapy with the calcium channel blocker verapamil improved treadmill exercise time in patients with symptomatic heart failure and normal LV ejection fractions. The effect of verapamil on SBP during exercise was not measured. Similarly, short-term verapamil therapy increased exercise tolerance in patients with diastolic dysfunction due to hypertrophic cardiomyopathy (22). However, the effects of losartan and verapamil in these studies cannot be directly compared owing to the different selection criteria used. Furthermore, the effect of long-term therapy of diastolic dysfunction has not been assessed.

On the basis of isolated anecdotal experience, it has been suggested that ACE inhibitors should be avoided in elderly patients with diastolic dysfunction because of hypertensive LV hypertrophy (23). Our observations demonstrate that Ang II receptor blocker with losartan was well tolerated and improved exercise tolerance and quality of life in the patients in our study, many of whom were elderly, some with LV hypertrophy.

Study limitations. We measured exercise tolerance using the Modified Bruce Protocol of treadmill exercise (14). The duration of exercise in our study may have been influenced by the patients' motivation and subjective interpretation of their symptoms during exercise. These confounding effects should have reduced our ability to observe a benefit from losartan therapy. Alternatively, the lower SBP during losartan exercise may have influenced the examiner to push the subject further. However, exercise tolerance assessed by the quality of life questionnaire also improved with losartan.

Sixteen of the patients in our study were taking a variety of common antihypertensive medications, including beta-adrenergic blocking agents, ACE inhibitors, and calcium channel blockers. These medications were continued during the study. Thus, the benefit we observed with losartan occurred in addition to any beneficial effects of these other medications. It is also possible that some of the beneficial effect was due to an interaction of losartan and the baseline medications that were continued throughout the study. Although the patients' mean BP was 143/79 mm Hg at rest on their baseline medication and not reduced further at rest by the addition of losartan, it is possible that more aggressive antihypertensive therapy with agents other than an Ang II receptor blocker could have produced a similar improvement in exercise tolerance.

Several other potential limitations should be considered. We studied the effect of two weeks of therapy. Thus, it is possible that the beneficial effects of losartan would not persist with a longer duration of therapy. A two-week washout period was used. Although the washout period exceeds the half-life of losartan (2.1 h) and its active metabolite (6.3 h) by more than 50-fold (24), we cannot

Table 4. Effect of Losartan on Echo-Doppler Measures of Diastolic Performance

	Baseline	Placebo	Losartan
Mitral E/A	0.75 ± 0.13	0.87 ± 0.22	0.85 ± 0.14
E Deceleration Time (ms)	197 ± 31	186 ± 47	205 ± 35
IVRT (ms)	89 ± 22	79 ± 19	81 ± 17
LV EF	62 ± 9.3	60.3 ± 10	68.9 ± 10.1
LV EDV (ml)	87.4 ± 25.6	91.8 ± 36.1	81.9 ± 22.4

Values are mean ± SD.

exclude a lingering effect in those patients that received losartan first. Finally, the large majority (16 of 20) of our subjects were women. This may result from a higher prevalence of diastolic dysfunction in women (25).

Conclusions. We found in patients with Doppler-echocardiographic evidence of mild LV diastolic dysfunction and a marked hypertensive response to exercise that treatment with an Ang II receptor blocker blunted the increase in systolic BP with exercise, improved exercise tolerance and enhanced the quality of life.

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